

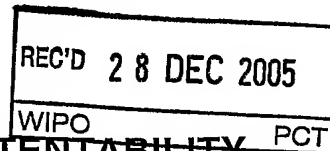
PATENT COOPERATION TREATY


PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference PC25833A	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/IB2005/000221	International filing date (day/month/year) 26.01.2005 ✓	Priority date (day/month/year) 02.02.2004 ✓
International Patent Classification (IPC) or national classification and IPC C07D453/02		
Applicant PFIZER PRODUCTS INC. et al. ✓		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet. ✓</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand 21.03.2005 ✓	Date of completion of this report 23.12.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Härtinger, S Telephone No. +49 89 2399-	



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/IB2005/000221

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-33 as originally filed

Claims, Numbers

1-10 as originally filed

Drawings, Sheets

1/1 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/IB2005/000221

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-10
	No: Claims	
Inventive step (IS)	Yes: Claims	1-10
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-10
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and /or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item V:

1. The application relates to a process for preparing camphersulfonic acid (CSA) salt of 1-(2S,3S)-2-Benzhydryl-N-(5-ter-butyl-2-methoxybenzyl)quinuclidin-3-amine having the formula Ib. The process makes use of intermediates in the CSA salt form, of which the preferred intermediate Via is likewise claimed.

The relevant prior art is represented by the following documents.

- D1: WO 97/03984 A (PFIZER INC; TICKNER, DEREK, L; MELTZ, MORGAN) 6 February 1997 (1997-02-06)
- D2: US-B1-6 222 038 (ITO FUMITAKA ET AL) 24 April 2001 (2001-04-24)
- D3: WARAWA E J ET AL: "Quinuclidine chemistry. 4. Diuretic properties of cis-3-amino-2-benzhydrylquinuclidine." JOURNAL OF MEDICINAL CHEMISTRY. JUN 1975, vol. 18, no. 6, June 1975 (1975-06), pages 587-593, XP002327149 ISSN: 0022-2623
- D4: US-B1-6 255 320 (QUALLICH GEORGE JOSEPH ET AL) 3 July 2001 (2001-07-03)

The cited prior art makes use of CSA in catalytic amounts to achieve the amination of 3-ketoquinuclidine. CSA has also been used for the resolution of racemic end-products. While enantiomerically pure cis-intermediates of the type presently used are known in the art, none of the cited documents discloses CSA quinuclidine salts, which were pulled through a multi-step synthesis procedure. By consequence, the claimed processes and intermediate (VIa) appear to be novel in the sense of Art. 33(2) PCT.

The most pertinent prior art is represented by D1, D2 and D3. D1 teaches the use of CSA for the resolution of racemic 2-Benzhydryl-N-(5-iso-propyl-2-methoxybenzyl)quinuclidin-3-amine. The said resolution step only occurs at the end of the multi-step procedure and does not involve the transformation of CSA intermediates. While the use of enantiomeric intermediates, such as 2-Benzhydryl-N-benzyl)quinuclidin-3-amine and 2-Benzhydryl-quinuclidin-3-amine, are suggested for the production of 2S,3S-cis end products (eg. page 8 of D1), the use of intermediates in salt form is not taught. Similarly, the documents D2 and D3 teach, that

enantiomerically pure cis-intermediates may be pulled through analogous multi-step procedures, whereby the enantiomers have been obtained by chromatography or by formation with chiral acids at the final synthesis step. The skilled person, who was looking to find an alternative process for the synthesis of known product (I), was therefore left without guidance, when solving the problem by the use of the present CSA quinuclidine intermediates (VIa) and (VII). The claimed processes and the intermediates, which are essential for proposed solution, are therefore considered to be the result of not obvious modifications of the prior art. The claimed subject-matter appears therefore to meet the requirement of Art. 33(3) PCT.

Re Item VI:

1. The international patent application D5 (= WO 2004/035575 A, PFIZER PRODOUCTS, INC; DSM PHARMACEUTICALS, INC; NUGENT, THOMAS, C; SE, 2004-04-29) has been published between the priority and filing date of the present application. The free amino intermediates and the CSA salt of final products disclosed therein do therefore not form part of the state of the art as defined in the PCT. By consequence, D5 has been disregarded from further considerations.